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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/805,449	03/13/2001	Fu-Tong Liu	051501/027 8726	9750

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EXAMINER	
LANDSMAN, ROBERT S	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 01/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/805,449	LIU ET AL.	
	Examiner	Art Unit	
	Robert Landsman	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 36-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12 and 36-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Formal Matters

A. Claims 1-47 are pending in this application. Claims 1-12 and 36-47 are the subject of this Office Action.

B. All Statutes under 35 USC not found in this Office Action can be found, cited in full, in a previous Office Action.

2. Claim Rejections - 35 USC § 112, first paragraph – written description

A. Claims 1-12 and 36-47 remain rejected under 35 USC 112, first paragraph, for the reasons already of record on page 3 of the Office Action dated 8/11/03. Applicants argue that the structure of galectin-3 was known at the time of the present invention and the carbohydrate (CHO) binding domain (lectin domain), which mediates binding to receptor, is located in C-terminal region of the galectin-3 molecule and deletion of this region impairs activity. It was also well-known that the N-terminal half of galectin-3 mediates multimerization. Therefore, in view of the knowledge in the art, one skilled in the art would know various galectin-3 functional domains, and that a CHO binding galectin-3 fragment lacking a functional multimerization domain would bind receptor but fail to multimerize.

This argument has been considered, but is not deemed persuasive. Respectfully, these limitations are not in the claims. Therefore, Applicants' invention is not limited to making changes in these known regions and Applicants have not adequately described any other regions which could be altered to modulate cell migration. Applicants have only disclosed one example of a modified galectin-3 in the specification (a C-terminal galectin-3 fragment) which inhibited monocyte migration induced by full-length galectin-3 (page 32, lines 7-16). No other modified galectin-3 molecules were further described in the specification.

Applicants further argue that, given that galectin-3 activity is enhanced by galectin-3 antibodies, these antibodies can therefore stimulate cell migration mediated by galectin-3. In support of this position, Applicants submitted a sworn Declaration under 37 C.F.R. 1.132 by Dr. Liu, the inventor of the subject application. Dr. Liu states that he is the first author of Exhibit 1 and has an intimate understanding of the data presented in Exhibit 1 (Exhibit 2, paragraphs 6 and 7). Dr. Liu concludes that based upon the studies described in Exhibit 1 and his expertise in the relevant art, that one or more of the antibodies described in Exhibit 1 is expected to stimulate cell migration as claimed thus, an adequate written description for such galectin-3 antibodies is provided.

This argument and the Declaration, respectfully, have also been considered, but are not deemed persuasive. According to the Declaration, the studies described in Exhibit 1 concern seven antibodies that bind galectin-3. Three of these antibodies, A3A12, B3A12 and C1C2 were demonstrated to activate galectin-3, as assessed by enhanced galectin-3 binding to IgE and enhanced galectin-3 hemagluttinating activity. One of these antibodies, A3A12, significantly enhanced superoxide (SO) production of neutrophils. Based on the data in Exhibit 1, Dr. Liu concluded that at least one of the seven antibodies described in Exhibit 1 is expected to stimulate cell migration in accordance with the claimed methods. However, it is unclear as to which of these antibodies would be expected to modulate cell migration. It cannot be determined from Exhibit 1 or the Declaration by Dr. Liu how it would be expected that an antibody which affects galectin-3 binding to IgE, enhances hemagluttinating activity or SO production would be expected to stimulate cell migration. Given these statements and data, alone, the Examiner is unable to determine a nexus between the activities taught in the prior art (Exhibit 1) and the claimed invention. Furthermore, if seven antibodies were taught and it is only believed that as few as one is able to stimulate cell migration, these antibodies have not been adequately described. No other species are described, or structurally contemplated, within the instant specification. Therefore, one skilled in the art cannot reasonably visualize or predict which antibodies (or C-terminal fragments) which would structurally characterize the genus of antibodies or "galectin-3 binding polypeptides" (or galectin-3 fragments) claimed, because it is unknown and not described what structurally constitutes any different antibodies which meet the claim limitations; thereby not meeting the written description requirement under 35 USC 112, first paragraph.

B. Claims 1-12 and 36-47 are rejected under 35 USC 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These are genus claims. The claims recite modulating the migration of all cells by use of galectin-3, or fragments/subsequences thereof. The specification and claims do not indicate what distinguishing attributes are shared by the members of the genus. It is believed that these cells must all express a galectin-3 receptor. However, the scope of the claims includes numerous structural variants (i.e. cells), and the genus is highly variant because a significant number of cell types is permitted. The specification and claims do not provide any guidance as to what cells migration can be modulated by galectin-3. Features that could distinguish cells in the genus from others in the class are missing from the disclosure.

No common attributes identify the members of the genus, other than the assumption that the cells must express the galectin-3 receptor, *which is not necessarily a requirement*. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, "cell" alone are insufficient to describe the genus.

Furthermore, Applicants have not provided adequate written description as to how to modulate cell migration in vivo in a subject. The claims recite, for example, increasing monocyte migration to an infection, a tumor or an inflammatory site. However, Applicants have not described how to practice these methods. In other words, it is not understood how administering galectin-3 to a wound site would permit the migration of cells to that site. It would be expected that galectin-3 would diffuse upon administration to a site. Therefore, it is not understood how a sufficient concentration of galectin-3 could be administered in order to allow for the migration of cells to an intended site.

One of skill in the art would reasonable conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus at the time the invention was made.

3. Claim Rejections - 35 USC § 112, first paragraph – scope of enablement

A. Claims 5, 6 and 40 remain rejected under 35 USC 112, first paragraph, for the reasons already of record on pages 4-5 of the Office Action dated 8/11/03. Applicants argue that the specification discloses both in vitro and in vivo cell migration assays (see, page 28, line 3, to page 29, line 6). The specification exemplifies these assays for intact galectin-3, a C-terminal galectin-3 fragment and a galectin-3 antibody, B2C10 (page 29, line 22, to page 32, line 16; and page 34, line 18, to page 36, line 2). Thus, in view of the fact that the specification discloses routine assays for identifying galectin-3 fragments/subsequences that modulate cell migration in vitro and in vivo, one skilled in the art could obtain such galectin-3 fragments/subsequences without undue experimentation.

This argument has been considered, but is not deemed persuasive. While the specification does disclose assays for identifying fragments and subsequences of galectin-3, Applicants have not provided sufficient examples of these fragments and subsequences. Applicants have only provided guidance and working examples of one C-terminal galectin-3 fragment and one galectin-3 antibody, B2C10. Therefore, even though an assay is disclosed for identifying these fragments and subsequencs, given the relatively limited teachings in the art about the functional domains of glaectin-3 and the minimal guidance and

working examples of these fragments and subsequences, it is unpredictable to the artisan which of these fragments and subsequences would be able to modulate cell migration. Furthermore, due to this limited guidance, it is not predictable which fragments and subsequences would be able to inhibit cell migration and which would be able to stimulate cell migration. Applicants do argue that to produce a galectin-3 subsequence that inhibits cell migration, the skilled artisan would know to delete all or a part of the N-terminal multimerization domain and to retain a functional lectin domain. To produce a galectin-3 subsequence that stimulates cell migration, the skilled artisan would know to delete amino acids outside of the lectin and multimerization domains in order to maintain activity. Thus, the skilled artisan would know the galectin-3 sequences that may be deleted or retained in order to produce galectin-3 subsequences/fragments that stimulate or inhibit cell migration and that such galectin-3 subsequences/fragments could readily be produced without undue experimentation. However, though Applicants have provided limited guidance as to the general regions of galectin-3 which may be involved in galectin activity and, perhaps, cell migration, Applicants have still not defined the residues outside these regions (lectin and multimerization domains) which are critical to inhibit cell migration, nor, except for the demonstration that the lectin domain is required for cell migration (page 32 of the specification), have Applicants demonstrated which other regions are required for function.

B. Claims 1-12 and 36-47 remain rejected under 35 USC 112, first paragraph, for the reasons already of record on page 5 of the Office Action dated 8/11/03. Applicants argue that the specification discloses both in vitro and in vivo cell migration assays (see, page 28, line 3, to page 29, line 6). The specification exemplifies these assays for intact galectin-3, a C-terminal galectin-3 fragment and a galectin-3 antibody, B2C10 (page 29, line 22, to page 32, line 16; and page 34, line 18, to page 36, line 2). Thus, in view of the fact that the specification discloses routine assays for identifying galectin-3 fragments/subsequences that modulate cell migration in vitro and in vivo, one skilled in the art could obtain such galectin-3 fragments/subsequences without undue experimentation.

This argument has been considered, but is not deemed persuasive. While the specification does disclose assays for identifying fragments and subsequences of galectin-3, Applicants have not provided sufficient examples of these fragments and subsequences. Applicants have only provided guidance and working examples of one C-terminal galectin-3 fragment and one galectin-3 antibody, B2C10. Therefore, even though an assay is disclosed for identifying these fragments and subsequencs, given the relatively limited teachings in the art about the functional domains of glaectin-3 and the minimal guidance and working examples of these fragments and subsequences, it is unpredictable to the artisan which of these

fragments and subsequences would be able to modulate cell migration. Furthermore, due to this limited guidance, it is not predictable which fragments and subsequences would be able to inhibit cell migration and which would be able to stimulate cell migration.

Furthermore, Applicants argue that the specification discloses that both N-terminal and C-terminal domains of galectin-3 are important for galectin-3 activity (page 10, lines 22-25; page 15, lines 11-13). The C-terminal lectin domain mediates CHO binding (page 31, lines 17-18) and the specification exemplifies a C-terminal galectin-3 fragment that inhibits galectin-3 induced cell migration (page 32, lines 7-16). This argument has also been considerer, but is not deemed persuasive. Again, though Applicants have provided limited guidance as to the general regions of galectin-3 which may be involved in galectin activity and, perhaps, cell migration, Applicants have still not defined the residues outside these regions (lectin and multimerization domains) which are critical to inhibit cell migration, nor, except for the demonstration that the lectin domain is required for cell migration (page 32 of the specification), have Applicants demonstrated which other regions are required for function.

C. Claims 1-12 and 36-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of galectin-3 to stimulate monocytes, does not reasonably provide enablement for the use of galectin-3, or fragments/subsequences thereof, to stimulate the migration of cells other than monocytes, nor does the specification provide enablement for the claimed methods to treat the claimed conditions, such as inflammation, infection or cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

First, the breadth of the claims is excessive with regard to claiming methods of modulating all cells by using galectin-3. Applicants provide no guidance or working examples of cells other than monocytes which can be affected by galectin-3. Furthermore, it is not predictable to one of ordinary skill in the art which cells could be modulated by galectin-3, or fragments/subsequences thereof, other than monocytes.

Similarly, Applicants have not provided any guidance or working examples of how to administer galectin-3 to a site in a sufficient quantity and for a sufficient amount of time in order to have the intended effect of treating inflammation, infection or a tumor. It would not be predictable to the artisan how to administer galectin-3 to a particular site in a sufficient concentration for a sufficient time to treat the intended condition. It would be expected that galectin-3 would diffuse from the intended treatment site.

Therefore, due to the excessive breadth of the claims regarding methods of modulating all cells other than monocytes, along with the lack of guidance and working examples of these cells, or how to administer this compound to an intended site for an intended use, as well as the lack of predictability to one of ordinary skill in the art which cells other than monocytes can be modulated, or how to successfully administer this compound, leads the Examiner to hold that undue experimentation is necessary to practice the invention as claimed.

4. Claim Rejections - 35 USC § 112, second paragraph

A. Applicants requested clarification of the statement in the Office Action at page 3B, second paragraph regarding the statement "Applicants have argued that inactive galectin-3 proteins can be made which can bind to the galectin-3 receptor, but which do not modulate cell migration." Applicants believe that the word "not" is a typographical error. Applicants are correct.

B. Claims 1-12 and 36-47 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: a positive recitation of how to perform the claimed methods. The claims simply state, for example, "a method of modulating cell migration by administering a modulating amount of galectin-3, or fragment thereof." This, respectfully, is similar to saying "a method of driving a car by sitting in the car and driving it." There is no further instruction on how to perform the claimed method.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Landsman whose telephone number is (703) 306-3407. The examiner can normally be reached on Monday - Friday from 8:00 AM to 5:00 PM (Eastern time) and alternate Fridays from 8:00 AM to 5:00 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Fax draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Robert Landsman, Ph.D.
Patent Examiner
Group 1600
January 15, 2004

ROBERT LANDSMAN
PATENT EXAMINER